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Abstract

Under the action of growth factors, proliferating and nonproliferating hematopoietic stem cells differentiate and divide, so as to produce blood cells. Growth factors act at different levels in the differentiation process, and we consider their action on the mortality rate (apoptosis) of the proliferating cell population. We propose a mathematical model describing the evolution of a hematopoietic stem cell population under the action of growth factors. It consists of a system of two age-structured evolution equations modelling the dynamics of the stem cell population coupled with a delay differential equation describing the evolution of the growth factor concentration. We first reduce our system of three differential equations to a system of two nonlinear differential equations with two delays and a distributed delay. We investigate some positivity and boundedness properties of the solutions, as well as the existence of steady states. We then analyze the asymptotic stability of the two steady states by studying the characteristic equation with delay-dependent coefficients obtained while linearizing our system. We obtain necessary and sufficient conditions for the global stability of the steady state describing the cell population's dying out, using a Lyapunov function, and we prove the existence of periodic solutions about the other steady state through the existence of a Hopf bifurcation.

Keywords: Age structured model, differential equations, distributed delay, asymptotic stability, Lyapunov function, Hopf bifurcation, blood cells model, stem cells, growth factors.

1 Introduction

Hematopoietic stem cells are undifferentiated cells, located in the bone marrow, with unique capacities of differentiation (the ability to produce cells committed to one blood cell lineage: white cells, red blood cells or platelets) and self-renewal (the ability to produce a

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cell with the same properties). These cells are at the root of the blood production process, called hematopoiesis. They produce committed stem cells which in turn will differentiate in precursor cells and, eventually, blood cells, which enter the bloodstream.

The differentiation of hematopoietic stem cells in one of the three blood cell type is mediated by growth factors. They are molecules acting like hormones in the blood production process, playing an activator / inhibitor role. A control operates between the number of circulating blood cells (red blood cells, white cells and platelets) and the production of growth factors: the less there are circulating blood cells, the more there are growth factors produced. When the number of circulating blood cells is large enough, the release of growth factors decreases. Growth factors act at every cell compartment (stem cells, committed stem cells, precursors), mainly either by triggering the cell proliferation or by decreasing the cell mortality (especially for proliferating cells), see for example [19, 22].

The probably most known growth factor is erythropoietin, or Epo, produced by the kidneys to trigger the production of red blood cells. Different growth factors act to help the production of red blood cells, white cells and platelets.

To our knowledge, mathematical modelling of hematopoietic stem cells dynamics has been first performed by Mackey [23, 24]: he proposed a system of two delay differential equations describing the evolution of a stem cell population divided in two compartments, proliferating and nonproliferating cells. The model in [23] has been recently studied by Pujo-Menjouet and Mackey [32] and Pujo-Menjouet et al [31]. In these works, the authors showed the existence of a Hopf bifurcation that destabilizes the unique nontrivial steady state of the model, leading to periodic solutions, and stressed the influence of each parameter (mortality rates, introduction rate in the proliferating phase, cell cycle duration) of the model on the amplitudes and periods of oscillating solutions.

Bernard et al [11, 12] adapted the model of Mackey [23] to study the production of white cells, and Colijn and Mackey [15, 16] generalized the works in [11] to model the production of all blood cell types.

In the above cited works, the models always take the form of a system of nonlinear differential equations with a discrete delay, describing a constant cell cycle duration. Adimy et al [3, 5, 6] analyzed the dynamics of the model in [23] assuming that all cell do not divide at the same age and so the cell cycle duration is distributed according to a density function. The authors obtained the existence of a Hopf bifurcation and applied their results to periodic chronic myelogenous leukemia, a cancer of white blood cells known for exhibiting, in some cases, very long periods oscillations compared to cell cycle durations.

The model in [23] has also been modified to take into account a structure in the stem cell population (the structure being either age, maturity, or age-maturity) and the resulting models have been widely studied. We mention the papers by Mackey and Rey [25, 26, 27], Mackey and Rudnicki [28, 29], Dyson et al [17, 18], Adimy and Pujo-Menjouet [8], Adimy and Crauste [1, 2], Adimy et al [4], and the references therein. In these works, considering different assumptions about the cell cycle duration (constant, distributed according to a density, maturity-dependent), the influence of pluripotent hematopoietic stem cells (the less mature stem cells) on the stability of the entire process of hematopoiesis has been pointed out.

In 1995 and 1998, Bélair et al [9] and Mahaffy et al [30] considered an age structured system of two equations, coupled with a differential equation, modelling the dynamics of hematopoietic stem cells under the action of growth factors. They assumed that the introduction rate in the proliferating phase depended on the growth factor concentration and, applying their model to the production of red blood cells (with erythropoietin as a growth factor), they managed to model normal hematopoiesis but stressed some difficulties to describe pathological cases (in particular, they obtained the existence of oscillating solutions with

periods that can be related to some data observed in patients with autoimmune hemolytic anemia, a disease triggering oscillations of red blood cells, but their results were limited by the lack of experimental data). We also mention a work by Adimy et al. [7], which deals with a system of three delay differential equations describing the production of blood cells under the action of growth factors. As in [9, 30], growth factors are assumed to act on the rate of introduction in the proliferating phase. The authors apply their model to some periodic hematological diseases, in particular chronic myelogenous leukemia, and obtain the existence of very long periods oscillations for short cell cycle durations.

In this work, we consider the action of growth factors on the mortality rate of the proliferating phase, known as apoptosis (a programmed cell death). To our knowledge, this assumption has never been used in hematopoiesis modelling, although it is mentioned in specialized literature (see, for example, [34]). Growth factors are known to decrease, in some cases, the apoptotic rate so as to bring more cells to the division, and then increase the blood cell production [19, 22, 37]. This assumption, contrary to the one saying that growth factors act on the introduction rate from the nonproliferating phase to the proliferating one [7, 9, 30], leads to a model with distributed delay, whose analysis is more complicated.

We model the dynamics of hematopoietic stem cells with an age structured model describing the evolution of proliferating and nonproliferating stem cells, coupled with a delay differential equation describing the production of growth factors. Our model can be reduced to a system of delay differential equations with two different discrete delays (corresponding to the cell cycle duration and the time needed to release growth factors in the bloodstream), and a distributed delay (describing the action of growth factors on the apoptosis rate). While studying the local asymptotic stability of the steady states of our model, we are led to a characteristic equation with delay-dependent coefficients. In that case, Beretta and Kuang [10] developed a method that allows the study of the stability for such equations. Moreover, due to the presence of two different delays, we use an approach proposed by Wei and Ruan [36] and Ruan and Wei [33], which consists in analyzing the stability when one delay is equal to zero and deduce the stability when both delays are nonzero with analytical tools.

In the next section, we present our model, which takes the form of an age structured system of two equations, with nonlinear boundary conditions, coupled with a differential equation with delay. We reduce it to a system of two delay differential equations using an integration over the age variable and the method of characteristics. In section 3, we study the positivity and boundedness properties of the solutions, and we determine steady states of our model. Then, in section 4, we linearize the system about one of its steady states, in order to perform the analysis of the local asymptotic stability, and we deduce the characteristic equation. In section 5, we first obtain necessary and sufficient condition for the global asymptotic stability of the steady state describing the cell population's dying out with a saturation of the growth factor concentration, using a Lyapunov function. Then we prove the existence of a Hopf bifurcation for the other steady state, by studying the associated characteristic equation with delay-dependent coefficients. We conclude with a discussion.

2 Structured Model of Blood Production

Let consider a population of hematopoietic stem cells, located in the bone marrow. This population is divided in two compartments (see [13, 14]): proliferating and nonproliferating cells. Proliferating stem cells are actually performing the main stages of cell cycle (growth, DNA synthesis), in order to divide during mitosis in two daughter cells. These latter immediately enter the nonproliferating phase, also known as resting phase, at birth. The resting phase is a quiescent stage with respect to growth and maturation.

Nonproliferating cells are assumed to differentiate at a constant rate $\delta > 0$, which can also take some natural mortality into account, and they are introduced in the proliferating phase whenever during their life with a rate β, which is supposed to depend on the total population of nonproliferating cells (see Mackey [23, 24], Mackey and Rudnicki [28, 29] or Pujo-Menjouet et al [31, 32]).

As soon as a cell enters the proliferating phase, it is committed to divide a time τ later. We assume (see [23, 28, 31, 32]) that the duration of the proliferating phase is the same for all cells, so τ is constant. Thus, this parameter describes an average duration of the cell cycle.

The number of proliferating cells is controlled by a particular mortality rate, known as apoptosis. It is in fact a programmed cell death, aimed to eliminate deficient cells. We assume that this mortality rate depends upon the concentration of growth factors, which can increase or decrease the mortality in the proliferating phase (see [19, 22, 37]). Some growth factors are known to reduce the apoptosis rate, leading to a more important production of blood cells through division. This is the case for Epo: the more there is Epo released, the more the apoptosis rate decreases. Hence we assume in this work that the apoptosis rate, denoted by γ, is a positive function of the concentration of growth factor, denoted by E. Since an increase in the growth factor concentration leads to a decrease of the apoptosis rate, we assume that γ is a decreasing function of E.

Denote by $n(t,a)$ and $p(t,a)$ the populations of nonproliferating and proliferating hematopoietic stem cells, respectively, which have an age a at time t. Note that the age represents the time spent by a cell in one of the two phases. In the resting phase, the age variable ranges from 0 to infinity, whereas in the proliferating phase it varies between 0 and τ. The evolution of the hematopoietic stem cell population is described by the following system of age-structured partial differential equations,

$$\frac{\partial n}{\partial t}(t,a) + \frac{\partial n}{\partial a}(t,a) = -\delta n(t,a) - \beta(N(t))n(t,a), \tag{1}$$

$$\frac{\partial p}{\partial t}(t,a) + \frac{\partial p}{\partial a}(t,a) = -\gamma(E(t))p(t,a), \tag{2}$$

where $N(t)$ denotes the total population of resting cells, that is

$$N(t) = \int_0^{+\infty} n(t,a)da,$$

and $E(t)$ is the growth factor concentration.

The introduction rate β is assumed to be a positive and decreasing function of N such that [23, 31]

$$\lim_{N\to+\infty} \beta(N) = 0.$$

Typically, β is a Hill function [23, 32], defined by

$$\beta(N) = \beta_0 \frac{\theta^s}{\theta^s + N^s}, \qquad \beta_0, \theta, s > 0. \tag{3}$$

The parameter β_0 represents the maximal rate of introduction in the proliferating phase, θ is the value for which β attains half of its maximum value, and s is the sensitivity of the rate of reintroduction.

System (1)–(2) is completed by boundary conditions (for $a = 0$) and initial conditions (for $t = 0$). The first ones describe the flux of cells entering each phase: new proliferating cells are nonproliferating cells introduced with a rate β, and new resting cells come from the

division of proliferating cells that have spent a time τ in the proliferating phase. Then the boundary conditions of (1)–(2) are

$$n(t,0) = 2p(t,\tau), \tag{4}$$

$$p(t,0) = \int_0^{+\infty} \beta(N(t))n(t,a)da = \beta(N(t))N(t). \tag{5}$$

We also assume that, for $t \geq 0$,

$$\lim_{a\to+\infty} n(t,a) = 0.$$

Initial conditions of (1)–(2) are given by nonnegative L^1 functions n_0 and p_0 such that

$$n(0,a) = n_0(a),\ a \geq 0 \qquad \text{and} \qquad p(0,a) = p_0(a),\ a \in [0,\tau]. \tag{6}$$

The concentration of growth factor $E(t)$ follows an evolution equation given by

$$E'(t) = -kE(t) + f(N(t-T)). \tag{7}$$

The coefficient k describes the disappearance rate of the growth factor while in bloodstream, whereas the function f acts as a negative feedback of the nonproliferating hematopoietic stem cell population on the production of growth factor. A more realistic hypothesis would be that the growth factor concentration is controlled by the number of circulating blood cells. However, we make the implicit hypothesis that the number of circulating blood cells is proportional to the number of nonproliferating hematopoietic stem cells, thus not taking into account an evolution equation satisfied by the circulating blood cell population and then assuming that f only depends upon $N(t)$. The time delay T represents the time needed to release growth factors in bloodstream after the stimulation by nonproliferating cells. This time is very short, about one hour [38], but a destabilization of the feedback loop may increase it.

We need to provide an initial condition for N on the interval $[-T,0]$, that is $N(\theta) = N_0(\theta)$, $\theta \in [-T,0]$, where N_0 is a given nonnegative continuous function on $[-T,0]$ such that $N_0(0) = \int_0^{+\infty} n_0(a)da$.

The evolution equation (7) of the growth factor concentration $E(t)$ has been introduced by Bélair et al [9] and Mahaffy et al [30]. However, in [9] and [30], the authors do not take into account the time needed to release growth factors, so $T = 0$ in their model.

Since f describes a negative feedback from the stem cell population on the growth factor concentration, we assume that f is positive and decreasing, and satisfies (see [9, 30])

$$\lim_{N\to+\infty} f(N) = 0.$$

In [9, 30], the function f is given by

$$f(N) = \frac{a}{1+KN^r}, \qquad \text{with } a, K, r > 0.$$

The system we consider, modelling the dynamics of a hematopoietic stem cell population under the action of growth factors, is then formed by equations (1) to (7). It consists of a system of age-structured differential equations, coupled with a delay differential equation. We are now going to check that system (1)–(6) reduces to a system of delay differential equations.

First, let see that using the method of characteristics (see Webb [35]), the solutions $p(t,a)$ of (2), (5) and (6), are given by

$$p(t,a) = \begin{cases} p_0(a-t)\exp\left(-\displaystyle\int_0^t \gamma(E(s))ds\right), & \text{if } 0 \leq t < a, \\ \beta(N(t-a))N(t-a)\exp\left(-\displaystyle\int_{t-a}^t \gamma(E(s))ds\right), & \text{if } 0 \leq a \leq t. \end{cases} \tag{8}$$

Denote by P the total population of proliferating stem cells,

$$P(t) = \int_0^\tau p(t,a)da.$$

Integrating system (1)–(2) with respect to the age variable, we obtain, for $t \geq 0$,

$$\begin{aligned} N'(t) &= -\delta N(t) - \beta(N(t))N(t) + n(t,0), \\ P'(t) &= -\gamma(E(t))P(t) + p(t,0) - p(t,\tau). \end{aligned} \tag{9}$$

Using (4) and (5), system (9) becomes

$$\begin{aligned} N'(t) &= -\delta N(t) - \beta(N(t))N(t) + 2p(t,\tau), \\ P'(t) &= -\gamma(E(t))P(t) + \beta(N(t))N(t) - p(t,\tau). \end{aligned} \tag{10}$$

Using (8), we finally obtain, for $0 \leq t < \tau$,

$$\begin{aligned} N'(t) &= -\delta N(t) - \beta(N(t))N(t) + 2p_0(\tau - t)\exp\left(-\int_0^t \gamma(E(s))ds\right), \\ P'(t) &= -\gamma(E(t))P(t) + \beta(N(t))N(t) - p_0(\tau - t)\exp\left(-\int_0^t \gamma(E(s))ds\right), \end{aligned}$$

and, for $t \geq \tau$,

$$\begin{aligned} N'(t) &= -\delta N(t) - \beta(N(t))N(t) \\ &\qquad + 2\beta(N(t-\tau))N(t-\tau)\exp\left(-\int_{t-\tau}^t \gamma(E(s))ds\right), \end{aligned} \tag{11}$$

$$\begin{aligned} P'(t) &= -\gamma(E(t))P(t) + \beta(N(t))N(t) \\ &\qquad - \beta(N(t-\tau))N(t-\tau)\exp\left(-\int_{t-\tau}^t \gamma(E(s))ds\right). \end{aligned} \tag{12}$$

Then we find that the total populations $N(t)$ and $P(t)$ satisfy a system of differential equations with distributed delay.

Using a method of steps, we obtain that the system formed by (10) and equation (7) has a unique nonnegative continuous solution defined on $[0, \max\{\tau, T\}]$. Hence we suppose that $t \geq \max\{\tau, T\}$.

Since equation (11) and the differential equation (7) do not depend on the proliferating cell population P, solution of (12), we will focus on the study of the system of delay differential equations formed by equations (7) and (11), that is

$$\begin{cases} N'(t) = -\delta N(t) - \beta(N(t))N(t) \\ \qquad\qquad + 2\beta(N(t-\tau))N(t-\tau)\exp\left(-\displaystyle\int_{-\tau}^0 \gamma(E(t+s))ds\right), \\ E'(t) = -kE(t) + f(N(t-T)), \end{cases} \tag{13}$$

defined for $t \geq \max\{\tau, T\}$, with initial conditions given on the interval $[0, \max\{\tau, T\}]$. We recall that β, γ and f are assumed to be positive and decreasing functions.

For each continuous initial condition, the system (13) has a unique continuous solution, defined for $t \geq \max\{\tau, T\}$ (see Hale and Verduyn Lunel [20], Theorem 2.3, page 44).

From now on, we make a translation of the initial conditions of system (13) so as to define them on the interval $[-\max\{\tau, T\}, 0]$, as it can be found in Hale and Verduyn Lunel [20].

In the next section, we focus on some properties of (13), such as positivity and boundedness of solutions, as well as the existence of steady states.

3 Properties of the Model and Existence of Steady States

We concentrate on the positivity and boundedness properties of the solutions $(N(t), E(t))$ of system (13).

First notice that using a classical variation of constant formula, we obtain, for $t \geq 0$,

$$E(t) = e^{-kt}E(0) + e^{-kt}\int_0^t e^{k\theta} f(N(\theta - T))d\theta. \tag{14}$$

We state and prove the following result.

Proposition 3.1. *The solutions of (13) are bounded and nonnegative. Moreover, either there exists $\bar{t} \geq 0$ such that $E(\bar{t}) \leq f(0)/k$ and then $E(t) \leq f(0)/k$ for all $t > \bar{t}$, or $\lim_{t\to+\infty} E(t) = f(0)/k$.*

Proof. We first check that the solutions N and E of (13) are nonnegative. Suppose that there exists $t_0 \geq 0$ such that $N(t) > 0$ for $t < t_0$ and $N(t_0) = 0$. Then, from (13), it follows that

$$N'(t_0) = 2\beta(N(t_0 - \tau))N(t_0 - \tau)\exp\left(-\int_{-\tau}^{0} \gamma(E(t_0 + s))ds\right) > 0,$$

since β is strictly positive. Consequently, $N(t)$ remains nonnegative for $t \geq 0$. Thus, using (14), the positivity of $E(t)$ follows from the fact that f is positive.

Now, we show that the solutions are bounded. Since f is bounded (f is decreasing, continuous and positive on $[0, +\infty)$ so $0 < f(N) \leq f(0)$ for $N \geq 0$), we deduce from (14) that

$$|E(t)| \leq e^{-kt}|E(0)| + \frac{f(0)}{k}\left(1 - e^{-kt}\right) \leq \max\left\{|E(0)|, \frac{f(0)}{k}\right\}.$$

Therefore E is bounded. Moreover, if $0 \leq E(0) \leq f(0)/k$, the above inequality implies that $E(t) \leq f(0)/k$ for all $t \geq 0$.

Consider the case $E(0) > f(0)/k$. Using (7), we easily obtain

$$E'(0) < -f(0) + f(N(-T)) \leq 0.$$

The same reasoning holds as long as $E(t) > f(0)/k$. Hence $E(t)$ is decreasing as long as $E(t) > f(0)/k$.

If there exists $\bar{t} \geq 0$ such that $E(\bar{t}) = f(0)/k$, then, using the same reasoning than in the first part of this proof, we obtain that $E(t) \leq f(0)/k$ for $t > \bar{t}$.

If $E(t) > f(0)/k$ for all $t \geq 0$, then $E'(t) < 0$ for all $t \geq 0$. Consequently $E(t)$ is a positive decreasing continuous function. Then $\lim_{t\to+\infty} E(t)$ exists and we show that it equals $f(0)/k$. Set $L = \lim_{t\to+\infty} E(t)$ and assume by contradiction that $L > f(0)/k$. From (7) and since f is bounded by $f(0)$, then

$$E'(t) + kE(t) = f(N(t - T)) \leq f(0).$$

Consequently, by taking the limit in the above inequality, we obtain $kL \leq f(0)$, which gives a contradiction. Hence $\lim_{t\to+\infty} E(t) = f(0)/k$.

We now prove that N is bounded. The proof is similar to the one in [6, 28]. Let $(N(t), E(t))$ be a solution of (13), and $C \geq 0$ be a bound of E.

Since β is positive, decreasing, and tends to zero at infinity, there exists $N_0 \geq 0$ such that $2e^{-\gamma(C)\tau}\beta(N) < \delta$ for $N > N_0$. Set

$$N_1 := 2e^{-\gamma(C)\tau}\frac{\beta(0)N_0}{\delta} \geq 0.$$

Let $N \geq N_1$ be fixed and $0 \leq y \leq N$. If $y \leq N_0$ then

$$2e^{-\gamma(C)\tau}\beta(y)y \leq 2e^{-\gamma(C)\tau}\beta(0)N_0 = \delta N_1 \leq \delta N.$$

If $y > N_0$, then

$$2e^{-\gamma(C)\tau}\beta(y)y < \delta y \leq \delta N.$$

Consequently,

$$2e^{-\gamma(C)\tau}\max_{0\leq y\leq N}\beta(y)y \leq \delta N, \qquad \text{for } N \geq N_1. \tag{15}$$

Now assume that $\limsup_{t\to+\infty} N(t) = +\infty$. Then there exists $t_0 > 0$ such that

$$N(t) \leq N(t_0) \quad \text{for } t \in [t_0 - \tau, t_0), \qquad \text{and} \qquad N(t_0) > N_1.$$

Using (13) and (15), it follows that

$$\begin{aligned} N'(t_0) &= -\delta N(t_0) - \beta(N(t_0))N(t_0) \\ &\quad +2\beta(N(t_0-\tau))N(t_0-\tau)\exp\left(-\int_{-\tau}^{0}\gamma(E(t_0+s))ds\right), \\ &\leq -\delta N(t_0) - \beta(N(t_0))N(t_0) + 2e^{-\gamma(C)\tau}\beta(N(t_0-\tau))N(t_0-\tau), \\ &\leq -\delta N(t_0) - \beta(N(t_0))N(t_0) + \delta N(t_0), \\ &\leq -\beta(N(t_0))N(t_0). \end{aligned}$$

Thus $N'(t_0) < 0$ and we obtain a contradiction. We deduce that N is bounded, and the proof is complete. □

From the above results, every solution $(N(t), E(t))$ of system (13) associated with nonnegative initial conditions is nonnegative and bounded.

We now investigate the existence of steady states of (13). Let $(\overline{N}, \overline{E})$ be a steady state of (13). It satisfies $d\overline{N}/dt = d\overline{E}/dt = 0$, that is

$$\begin{cases} \left[\delta + \beta(\overline{N})\right]\overline{N} = 2e^{-\gamma(\overline{E})\tau}\beta(\overline{N})\overline{N}, \\ k\overline{E} = f(\overline{N}). \end{cases} \tag{16}$$

A first steady state, $(0, f(0)/k)$, describing the stem cell population's dying out with a saturation of growth factor concentration, always exists. A nontrivial steady state $(\overline{N}, \overline{E})$, with $\overline{N} \neq 0, \overline{E} \neq 0$, would satisfy, from (16),

$$\left(2e^{-\gamma(f(\overline{N})/k)\tau} - 1\right)\beta(\overline{N}) = \delta \qquad \text{and} \qquad \overline{E} = \frac{f(\overline{N})}{k}. \tag{17}$$

Proposition 3.2. *Assume that*

$$\left(2e^{-\gamma(f(0)/k)\tau}-1\right)\beta(0)>\delta. \tag{18}$$

Then system (13) has two steady states: $(0, f(0)/k)$ *and* (N^*, E^*)*, with* $N^*>0$ *and* $E^*>0$ *solutions of (17).*

If (18) does not hold, then $(0, f(0)/k)$ *is the only steady state of system (13).*

Proof. Define, for $N\geq 0$, the function χ by

$$\chi(N)=2e^{-\gamma(f(N)/k)\tau}-1.$$

Since f and γ are decreasing, the mapping $N\mapsto\gamma(f(N)/k)$ is increasing. Thus χ is decreasing. Moreover,

$$\chi(0)=2e^{-\gamma(f(0)/k)\tau}-1 \qquad \text{and} \qquad \lim_{N\to+\infty}\chi(N)=2e^{-\gamma(0)\tau}-1.$$

One has to note that χ is not necessarily positive. In fact, either $2e^{-\gamma(0)\tau}-1>0$ and χ is positive, or $2e^{-\gamma(0)\tau}-1<0$ and there exists $\tilde{N}>0$, which is unique, such that $\chi(\tilde{N})=0$. Since χ is decreasing, $\chi(N)>0$ for $N<\tilde{N}$ and $\chi(N)<0$ for $N>\tilde{N}$, in this latter case.

First consider the case $2e^{-\gamma(0)\tau}-1>0$. Then χ is positive and decreasing on $[0,+\infty)$. Since β is also positive and decreasing on $[0,+\infty)$, then the function $\xi(N)=\chi(N)\beta(N)$ is decreasing and satisfies

$$\xi(0)=\left(2e^{-\gamma(f(0)/k)\tau}-1\right)\beta(0) \qquad \text{and} \qquad \lim_{N\to+\infty}\xi(N)=0.$$

Consequently, the equation $\xi(N)=\delta$ (which gives the existence of a positive steady state, see (17)) has a solution if and only if (18) holds true, and the solution is unique.

Suppose now that $2e^{-\gamma(0)\tau}-1<0$. Then, on the interval $(\tilde{N},+\infty)$, the function χ is negative and so is the function ξ. On the interval $[0,\tilde{N}]$, the function χ is positive and decreasing, so ξ is decreasing with $\xi(0)=\left(2e^{-\gamma(f(0)/k)\tau}-1\right)\beta(0)$ and $\xi(\tilde{N})=0$. The equation $\xi(N)=\delta$ then has a solution if and only if (18) holds true, and the solution then belongs to $[0,\tilde{N}]$.

This concludes the proof. □

Remark 1. *Condition (18) is equivalent to*

$$\beta(0)>\delta \qquad \textit{and} \qquad 0\leq\tau<\frac{1}{\gamma(f(0)/k)}\ln\left(\frac{2\beta(0)}{\delta+\beta(0)}\right):=\tau^*. \tag{19}$$

This describes the fact that the maximal introduction rate $\beta(0)$ *has to be larger than the mortality rate* δ *and the cell cycle duration* τ *cannot be too long for system (13) to exhibit an other steady state than the one describing the cell's dying out.*

Using the Implicit Function Theorem, one can check that the steady states $N^*(\tau)$ and $E^*(\tau)$ are continuously differentiable functions of $\tau\in[0,\tau^*)$. Moreover, $N^*(\tau)$ is decreasing, $E^*(\tau)$ is increasing, and $(N^*(0),E^*(0))=(\beta^{-1}(\delta),f(\beta^{-1}(\delta))/k)$ and

$$\lim_{\tau\to\tau^*}(N^*(\tau),E^*(\tau))=(0,f(0)/k).$$

In the following, we analyze the asymptotic behavior of the solutions of system (13) by studying the asymptotic stability of its steady states. To that aim, we deduce the linearized system of (13) and we obtain the associated characteristic equation in the next section.

4 Linearized System and Characteristic Equation

Let $(\overline{N}, \overline{E})$ be a steady state of system (13), that is, from Proposition 3.2, either $(\overline{N}, \overline{E}) = (0, f(0)/k)$ or $(\overline{N}, \overline{E}) = (N^*, E^*)$. We set

$$X(t) = N(t) - \overline{N} \qquad \text{and} \qquad Y(t) = E(t) - \overline{E}.$$

Assume that the functions β, γ and f are continuously differentiable. The linearized system of (13) around $(\overline{N}, \overline{E})$ is then

$$\begin{cases} X'(t) &= -\left(\delta + \overline{\beta}\right) X(t) + 2\overline{\beta} e^{-\gamma(\overline{E})\tau} X(t-\tau) \\ & \qquad\qquad -\alpha(\overline{N}, \overline{E}) e^{-\gamma(\overline{E})\tau} \displaystyle\int_{-\tau}^{0} Y(t+s)ds, \\ Y'(t) &= -kY(t) + f'(\overline{N}) X(t-T), \end{cases} \tag{20}$$

where

$$\overline{\beta} = \beta(\overline{N}) + \overline{N}\beta'(\overline{N}) \qquad \text{and} \qquad \alpha(\overline{N}, \overline{E}) = 2\overline{N}\beta(\overline{N})\gamma'(\overline{E}).$$

One can notice that $\alpha(\overline{N}, \overline{E}) \leq 0$, since γ is decreasing, with $\alpha(0, \cdot) = 0$.

If β is given by (3), with $s > 1$, the function $N \mapsto N\beta(N)$ is increasing for $N \leq \theta/(s-1)^{1/s}$ and decreasing for $N > \theta/(s-1)^{1/s}$. Therefore, in this case, $\overline{\beta}$ is nonnegative when $\overline{N}$ is close to zero and negative when $\overline{N}$ is large enough.

Set

$$A_0 = \begin{pmatrix} -\left(\delta + \overline{\beta}\right) & 0 \\ 0 & -k \end{pmatrix}, \qquad A_1 = \begin{pmatrix} 2\overline{\beta} e^{-\gamma(\overline{E})\tau} & 0 \\ 0 & 0 \end{pmatrix}$$

and

$$A_2 = \begin{pmatrix} 0 & -\alpha(\overline{N}, \overline{E}) e^{-\gamma(\overline{E})\tau} \\ 0 & 0 \end{pmatrix}, \qquad A_3 = \begin{pmatrix} 0 & 0 \\ f'(\overline{N}) & 0 \end{pmatrix}.$$

The characteristic equation associated with system (20) is then defined by

$$\det\left(\lambda I - A_0 - e^{-\lambda\tau} A_1 - \int_{-\tau}^{0} e^{\lambda\theta} d\theta A_2 - e^{-\lambda T} A_3\right) = 0, \qquad \lambda \in \mathbb{C}.$$

After calculations, this equation reduces to

$$(\lambda + k)(\lambda + \delta + \overline{\beta} - 2\overline{\beta} e^{-\gamma(\overline{E})\tau} e^{-\lambda\tau}) + f'(\overline{N})\alpha(\overline{N}, \overline{E}) e^{-\gamma(\overline{E})\tau} e^{-\lambda T} \int_{-\tau}^{0} e^{\lambda\theta} d\theta = 0. \tag{21}$$

We recall that the steady state $(\overline{N}, \overline{E})$ of (13) is locally asymptotically stable if all eigenvalues of (21) have negative real parts, and the stability can only be lost if pure imaginary roots appear. The steady state is unstable if eigenvalues with positive real parts exist.

One can note that in the general case, that is when (21) cannot be simplified, it is quite difficult to study the sign of the real parts of eigenvalues of (21), due to the presence of discrete and distributed delays as well as two different delays τ and T. In this case (see section 5.2), we will use an analytical approach proposed by Wei and Ruan [36] and Ruan and Wei [33], which consists in determining the stability of the steady state when one delay is equal to zero and deduce the stability when both delays are nonzero with analytical tools.

In the next section, we successively analyze the local asymptotic stability of the two steady states of system (13), $(0, f(0)/k)$ and (N^*, E^*), by studying the sign of the real parts of eigenvalues of (21).

5 Asymptotic Stability and Hopf Bifurcation

We concentrate, in this section, on the asymptotic stability of the steady states $(0, f(0)/k)$ and (N^*, E^*) of (13). We first show that $(0, f(0)/k)$ is globally asymptotically stable when it is the only steady state of (13), and that it becomes unstable when (N^*, E^*) appears. Then, we will focus on the local asymptotic stability of (N^*, E^*) and show the existence of a Hopf bifurcation that destabilizes the steady state and leads to the appearance of periodic solutions.

5.1 Global Asymptotic Stability of the Steady State $(0, f(0)/k)$

When $(\overline{N}, \overline{E}) = (0, f(0)/k)$, then $\alpha(0, f(0)/k) = 0$ and $\overline{\beta} = \beta(0)$, so (21) becomes

$$(\lambda + k)(\lambda + \delta + \beta(0) - 2\beta(0)e^{-\gamma(f(0)/k)\tau}e^{-\lambda\tau}) = 0. \tag{22}$$

It follows that $\lambda = -k$ is a negative real eigenvalue of (22) and all other eigenvalues λ are roots of

$$\Delta_0(\lambda) := \lambda + \delta + \beta(0) - 2\beta(0)e^{-\gamma(f(0)/k)\tau}e^{-\lambda\tau}. \tag{23}$$

Theorem 5.1. *The steady state $(0, f(0)/k)$ of (13) is globally asymptotically stable if and only if*

$$\left(2e^{-\gamma(f(0)/k)\tau} - 1\right)\beta(0) \leq \delta. \tag{24}$$

Proof. Define the set C of continuous functions mapping the interval $[-\max\{\tau, T\}, 0]$ into $\mathbb{R}^+$. For $(\varphi, \psi) \in C \times C$, we define

$$V(\varphi, \psi) = \int_0^{\varphi(0)} \theta\beta(\theta)d\theta + e^{-\tau\gamma(f(0)/k)} \int_{-\tau}^0 \left[\varphi(\theta)\beta(\varphi(\theta))\right]^2 d\theta.$$

One can note that V does not depend on ψ. Define

$$G = \left\{(\varphi, \psi) \in C \times C \ ; \ \psi \leq \frac{f(0)}{k}\right\}.$$

We are going to show that V is a Lyapunov function on G relative to system (13) (see [20]). V is continuous on the closure of G (with $\mathrm{Cl}(G) = G$) and

$$\dot{V}(\varphi, \psi) = \varphi'(0)\beta(\varphi(0))\varphi(0) + e^{-\tau\gamma(f(0)/k)}\left[\varphi(0)^2\beta(\varphi(0))^2 - \varphi(-\tau)^2\beta(\varphi(-\tau))^2\right].$$

Since, from (13),

$$\varphi'(0) = -(\delta + \beta(\varphi(0)))\varphi(0) + 2\beta(\varphi(-\tau))\varphi(-\tau)\exp\left(-\int_{-\tau}^0 \gamma(\psi(s))ds\right),$$

we deduce

$$\begin{aligned}\dot{V}(\varphi, \psi) = &\left[-\delta + (2e^{-\tau\gamma(f(0)/k)} - 1)\beta(\varphi(0))\right]\beta(\varphi(0))\varphi(0)^2 \\ &-e^{-\tau\gamma(f(0)/k)}\left[\varphi(0)\beta(\varphi(0)) - \varphi(-\tau)\beta(\varphi(-\tau))\right]^2 \\ &+2\varphi(0)\beta(\varphi(0))\varphi(-\tau)\beta(\varphi(-\tau))\left[\exp\left(-\int_{-\tau}^0 \gamma(\psi(s))ds\right) - e^{-\tau\gamma(f(0)/k)}\right].\end{aligned}$$

From condition (24) and since β is decreasing, for all $\varphi \in C$,

$$-\delta + (2e^{-\tau\gamma(f(0)/k)} - 1)\beta(\varphi(0)) \leq (2e^{-\tau\gamma(f(0)/k)} - 1)\left[\beta(\varphi(0)) - \beta(0)\right] \leq 0,$$

and since $(\varphi,\psi)\in G$, $\psi\leq f(0)/k$ so

$$\exp\left(-\int_{-\tau}^{0}\gamma(\psi(s))ds\right)-e^{-\tau\gamma(f(0)/k)}\leq 0.$$

Consequently $\dot{V}(\varphi,\psi)\leq 0$ for $(\varphi,\psi)\in G$, and V is a Lyapunov function on G.

Following the notations in [20], we define the set $S=\Big\{(\varphi,\psi)\in \mathrm{Cl}(G);\ \dot{V}(\varphi,\psi)=0\Big\}$. Let $(\varphi,\psi)\in S$ be given. Then

$$\varphi(0)=0\ \text{ and }\ \varphi(0)\beta(\varphi(0))=\varphi(-\tau)\beta(\varphi(-\tau))\ \text{ and }\ \int_{-\tau}^{0}\gamma(\psi(s))ds=\tau\gamma(f(0)/k).$$

It follows that

$$S=\left\{(\varphi,\psi)\in C\times C\ ;\ \varphi(0)=\varphi(-\tau)=0\ \text{ and }\ \psi\equiv\frac{f(0)}{k}\right\}.$$

Now let M be the largest set in S invariant with respect to (13). Then $(\varphi,\psi)\in M$ if and only if $(N_t^{\varphi},E_t^{\psi})\in S$ for all $t\geq 0$, where N_t^{φ} and E_t^{ψ} are defined by

$$N_t^{\varphi}(\theta)=N^{\varphi}(t+\theta)\quad\text{ and }\quad E_t^{\psi}(\theta)=E^{\psi}(t+\theta),\quad \theta\in[-\max\{\tau,T\},0],$$

and (N^{φ},E^{ψ}) is the unique solution of (13) associated with initial conditions (φ,ψ).

If $(\varphi,\psi)\in M$ we then obtain that

$$N^{\varphi}(t)=N^{\varphi}(t-\tau)=0\quad\text{ and }\quad E^{\psi}(t)=\frac{f(0)}{k},\quad\text{ for } t\geq 0.$$

It follows that $N^{\varphi}\equiv 0$ and $E^{\psi}\equiv f(0)/k$. Therefore $M=\{(0,f(0)/k)\}$.

Since V is a Lyapunov function on G and all solutions of (13) are bounded (see Proposition 3.1), then all solutions $(N(t),E(t))$ of (13) such that $E(t)\leq f(0)/k$ for t large enough (thus the solutions remain in G, from Proposition 3.1) converge to $(0,f(0)/k)$.

Now, let $(N(t),E(t))$ be a solution of (13) such that $E(t)>f(0)/k$ for all $t\geq 0$. From Proposition 3.1, $E(t)$ converges to $f(0)/k$. Let us check that $N(t)$ tends to zero in this case.

From Proposition 3.1, $E(t)$ is a decreasing and continuous function which tends to $f(0)/k$ at infinity. Therefore $\lim_{t\to+\infty}E'(t)=0$. Consequently, with (7), we obtain

$$\lim_{t\to+\infty}f(N(t-T))=f(0).$$

Since $f(N)<f(0)$ for $N>0$, we deduce that $N(t)$ tends to zero when t tends to infinity.

Eventually, all solutions of system (13) tends to $(0,f(0)/k)$ when condition (24) holds true.

Suppose now that condition (24) no longer holds, that is condition (18) holds true. Consider the function Δ_0, defined in (23), as a function of real λ. Then

$$\frac{d\Delta_0}{d\lambda}(\lambda)=1+2\beta(0)\tau e^{-\gamma(f(0)/k)\tau}e^{-\lambda\tau}>0.$$

Hence the function Δ_0 is increasing. Moreover,

$$\lim_{\lambda\to-\infty}\Delta_0(\lambda)=-\infty\qquad\text{and}\qquad\lim_{\lambda\to+\infty}\Delta_0(\lambda)=+\infty.$$

Consequently, Δ_0 has a unique real root, namely λ_0. Since (18) is fulfilled, then $\Delta_0(0)<0$ and $\lambda_0>0$, so Δ_0 has at least one root with positive real part, and the steady state $(0,f(0)/k)$ is unstable.

This concludes the proof. □

We have proved in Theorem 5.1 that the steady state $(0, f(0)/k)$ is globally asymptotically stable when (24) holds true, that is when it is the only steady state of system (13).

In the next section we focus on the local asymptotic stability of the steady state (N^*, E^*) of (13). In particular, we study the existence of a Hopf bifurcation that would destabilize the steady state and create periodic solutions.

5.2 Local Asymptotic Stability of (N^*, E^*) and Hopf Bifurcation

We assume, throughout this section, that condition (18) holds, or equivalently (19), to ensure the existence of the positive steady state (N^*, E^*) of system (13). From Theorem 5.1, the only other steady state of (13) is then unstable.

While studying the local asymptotic stability of (N^*, E^*), we have to determine the sign of the real parts of eigenvalues of (21). The presence of two different delays, τ and T, makes it more difficult than in the case of a single time delay. Hence, we are going to study the stability of (N^*, E^*) when one delay is equal to zero, and deduce the stability of (N^*, E^*) when both delays are nonzero using analytical tools (see [33, 36]). Due to the structure of equation (21), we are led to choose $T = 0$ in a first time, otherwise (if $\tau = 0$) there would be no exponential term anymore, in equation (21), and we would not be able to conclude to the stability when both τ and T are positive. The final result we will obtain will give the asymptotic stability of (N^*, E^*) for values of T smaller than the ones of τ. This is in agreement with biological meaning, since the time T needed to release growth factor after the stimulation is very short (about one hour) compared to cell cycle durations (between a few hours and several days).

From now on, we set $\beta^* = \overline{\beta} = \beta(N^*) + N^*\beta'(N^*)$.

We first check, in the next lemma, that (N^*, E^*) is locally asymptotically stable when $\tau = 0$, for all $T \geq 0$.

Lemma 5.1. *Assume that $\beta(0) > \delta$ and $\tau = 0$. Then the steady state (N^*, E^*) of system (13) is locally asymptotically stable for all $T \geq 0$.*

Proof. When $\tau = 0$ and $(\overline{N}, \overline{E}) = (N^*, E^*)$, the characteristic equation (21) becomes

$$(\lambda + k)(\lambda + \delta + \beta^* - 2\beta^*) = 0.$$

Hence, this equation has only two eigenvalues, $\lambda = -k < 0$ and $\lambda = \beta^* - \delta = N^*\beta'(N^*) < 0$. The conclusion follows. □

Let us assume, in a first time, that $T = 0$. Then, when $(\overline{N}, \overline{E}) = (N^*, E^*)$, equation (21) becomes

$$(\lambda + k)(\lambda + \delta + \beta^* - 2\beta^* e^{-\gamma(E^*)\tau} e^{-\lambda\tau}) + f'(N^*)\alpha^* e^{-\gamma(E^*)\tau} \int_{-\tau}^{0} e^{\lambda\theta} d\theta = 0, \qquad (25)$$

with $\alpha^* = \alpha(N^*, E^*) = 2N^*\beta(N^*)\gamma'(E^*)$.

Since (N^*, E^*) is locally asymptotically stable when $\tau = 0$, the stability can be lost as τ increases away from 0, with $\tau < \tau^*$ (τ^* defined in (19)), only if pure imaginary characteristic roots appear.

In the following, we investigate the existence of pure imaginary roots of (25). We first state and prove the following lemma.

Lemma 5.2. *$\lambda = 0$ is not a characteristic root of (21), and so neither it is of (25), when $(\overline{N}, \overline{E}) = (N^*, E^*)$.*

Proof. Assume that $\lambda = 0$ is an eigenvalue of (21) or (25). Then

$$k(\delta + \beta^* - 2\beta^* e^{-\gamma(E^*)\tau}) + f'(N^*)\alpha^* e^{-\gamma(E^*)\tau}\tau = 0.$$

From (17), since β is decreasing and $N^* > 0$, then

$$\delta + \beta^* - 2\beta^* e^{-\gamma(E^*)\tau} = \left(1 - 2e^{-\gamma(E^*)\tau}\right) N^* \beta'(N^*) > 0.$$

Moreover, since $\alpha^* < 0$ and f is decreasing, it follows that

$$k(\delta + \beta^* - 2\beta^* e^{-\gamma(E^*)\tau}) + f'(N^*)\alpha^* e^{-\gamma(E^*)\tau}\tau > 0,$$

and we obtain a contradiction. This ends the proof. □

Since $\lambda = 0$ is not an eigenvalue of (25), we deduce that λ is a characteristic root of (25) if and only if

$$\Delta(\lambda, \tau) = 0 \qquad \text{and} \qquad \lambda \neq 0,$$

where

$$\Delta(\lambda, \tau) := \lambda(\lambda + k)(\lambda + \delta + \beta^* - 2\beta^* e^{-\gamma(E^*)\tau} e^{-\lambda\tau}) + f'(N^*)\alpha^* e^{-\gamma(E^*)\tau}\left(1 - e^{-\lambda\tau}\right).$$

Simple computations give

$$\Delta(\lambda, \tau) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 + \left[b_1\lambda^2 + b_2\lambda + b_3\right] e^{-\lambda\tau},$$

with

$$\begin{array}{lllllll} a_1 &=& \delta + k + \beta^*, & & b_1 &=& -2\beta^* e^{-\gamma(E^*)\tau}, \\ a_2 &=& k(\delta + \beta^*), & & b_2 &=& -2k\beta^* e^{-\gamma(E^*)\tau}, \\ a_3 &=& f'(N^*)\alpha^* e^{-\gamma(E^*)\tau}, & & b_3 &=& -f'(N^*)\alpha^* e^{-\gamma(E^*)\tau}. \end{array}$$

Using (17), one can easily check that

$$a_1 + b_1 > 0, \qquad a_2 + b_2 > 0 \qquad \text{and} \qquad a_3 + b_3 = 0.$$

Remark 2. *One can notice that all coefficients a_i and b_i, $i = 1, 2, 3$, depend on the time delay $\tau \in [0, \tau^*)$, since the steady states N^* and E^* depend on τ (see (17)). We will not explicitly write the dependence of the coefficients a_i and b_i on τ in the following, but we will think of them as $a_i(\tau)$ and $b_i(\tau)$, $i = 1, 2, 3$.*

We now look for the existence of pure imaginary roots of (25). Let $\lambda = i\omega$, $\omega \in \mathbb{R}$ and $\omega \neq 0$, be such that $\Delta(i\omega, \tau) = 0$, $\tau \in [0, \tau^*)$. Separating real and imaginary parts of $\Delta(i\omega, \tau)$, we find

$$(-b_1\omega^2 + b_3)\cos(\omega\tau) + b_2\omega\sin(\omega\tau) = a_1\omega^2 - a_3, \tag{26}$$

$$b_2\omega\cos(\omega\tau) - (-b_1\omega^2 + b_3)\sin(\omega\tau) = \omega^3 - a_2\omega. \tag{27}$$

One can notice that if ω satisfies (26)–(27) then so is $-\omega$. Hence, we only look for positive ω satisfying (26)–(27), with $\tau \in [0, \tau^*)$.

Adding the squares of both sides of equations (26) and (27), we obtain that ω must satisfy

$$(-b_1\omega^2 + b_3)^2 + b_2^2\omega^2 = (a_1\omega^2 - a_3)^2 + \omega^2(\omega^2 - a_2)^2,$$

that is

$$\omega^6 + (a_1^2 - 2a_2 - b_1^2)\omega^4 + (a_2^2 + 2b_1b_3 - 2a_1a_3 - b_2^2)\omega^2 + a_3^2 - b_3^2 = 0. \tag{28}$$

We set

$$A(\tau) := a_1^2 - 2a_2 - b_1^2 \qquad \text{and} \qquad B(\tau) := a_2^2 + 2b_1b_3 - 2a_1a_3 - b_2^2. \tag{29}$$

Since $a_3 + b_3 = 0$, (28) reduces to

$$\omega^2 F(\omega^2, \tau) = 0,$$

with

$$F(X, \tau) = X^2 + A(\tau)X + B(\tau).$$

Hence, finding $\omega > 0$ solution of (28) is equivalent to determining positive roots X of $F(X, \tau)$, defined for $\tau \in [0, \tau^*)$. Since F is a second degree polynomial function in X, the following lemma is straightforward.

Lemma 5.3. *The polynomial function $F(X, \tau)$, $\tau \in [0, \tau^*)$, has positive roots if and only if*

$$B(\tau) < 0 \qquad or \qquad A^2(\tau) \geq 4B(\tau) \geq 0 > A(\tau). \tag{30}$$

If no $\tau \in [0, \tau^*)$ fulfills condition (30), then the characteristic equation (25) has no pure imaginary root. Consequently, from Lemma 5.1, all eigenvalues of (25) have negative real parts and the steady state (N^*, E^*) is locally asymptotically stable for all $\tau \in [0, \tau^*)$.

Remark 3. *We are going to check that condition (30) may be satisfied for τ in a nontrivial interval $I = [0, \overline{\tau})$, $0 < \overline{\tau} \leq \tau^*$, with an appropriate function β.*

Using the definitions of the coefficients a_i and b_i, $i = 1, 2, 3$, the coefficients $A(\tau)$ and $B(\tau)$, defined in (29), are given by

$$A(\tau) = (\delta + \beta^*)^2 + k^2 - \left(2\beta^* e^{-\gamma(E^*)\tau}\right)^2$$

and

$$\begin{aligned} B(\tau) = {} & k^2 N^* \beta'(N^*) \left[1 - 2e^{-\gamma(E^*)\tau}\right] \left[\delta + \beta^* + 2\beta^* e^{-\gamma(E^*)\tau}\right] \\ & + 2\alpha^* f'(N^*) e^{-\gamma(E^*)\tau} N^* \beta'(N^*) \left[2e^{-\gamma(E^*)\tau} - 1\right] - 2\alpha^* f'(N^*) e^{-\gamma(E^*)\tau} k. \end{aligned}$$

Since α^*, $f'(N^*)$ and $\beta'(N^*)$ are negative and $2e^{-\gamma(E^*)\tau} - 1 > 0$, a sufficient condition to obtain $B(\tau) < 0$ is

$$\delta + \beta^* + 2\beta^* e^{-\gamma(E^*)\tau} \leq 0. \tag{31}$$

Note that it is not easy to obtain sufficient conditions for $A(\tau) < 0$.

Condition (31) is equivalent to

$$\delta + (1 + 2e^{-\gamma(E^*)\tau})\beta(N^*(\tau)) \leq -(1 + 2e^{-\gamma(E^*)\tau})N^*(\tau)\beta'(N^*(\tau)).$$

One can notice that, for $\tau \in [0, \tau^*)$, $1 < 1 + 2e^{-\gamma(E^*)\tau} \leq 3$. Consequently, we look for $\tau \in [0, \tau^*)$ such that

$$\delta + 3\beta(N^*(\tau)) \leq -N^*(\tau)\beta'(N^*(\tau)).$$

Since $N^*(\tau)$ is a continuous and decreasing function of τ, with $0 < N^*(\tau) \leq \beta^{-1}(\delta)$, it is sufficient to find $x \in (0, \beta^{-1}(\delta)]$ such that

$$\delta + 3\beta(x) \leq -x\beta'(x). \tag{32}$$

With β given by (3), with $\theta = 1$, equation (32) is equivalent to

$$\delta X^2 + (2\delta + 3\beta_0 - s\beta_0)X + \delta + 3\beta_0 \leq 0 \qquad and \qquad X = x^s \in (0, (\beta^{-1}(\delta))^s]. \tag{33}$$

We set $\mu = \beta_0/\delta > 1$. Since $(\beta^{-1}(\delta))^s = (\beta_0 - \delta)/\delta$, (33) is equivalent to

$$X^2 + [2 + \mu(3-s)]X + 1 + 3\mu \leq 0 \qquad \text{and} \qquad X \in (0, \mu - 1]. \tag{34}$$

Then, after easy but tedious computations, one can see that there exists $\tilde{s} > 1$ such that, for $s \geq \tilde{s}$, the equation $X^2 + [2 + \mu(3-s)]X + 1 + 3\mu = 0$ has two roots $0 \leq X_1 < X_2$. Moreover, one can check that $X_2 > \mu - 1$, and $X_1 < \mu - 1$ if and only if $s > 4\mu/(\mu-1)$, where $4\mu/(\mu-1) \geq \tilde{s}$. Consequently, (34) is satisfied on an interval $(X_1, \mu - 1]$ provided that $s > 4\mu/(\mu-1)$. Going back to τ, and noticing that $N^*(0)^s = \mu - 1$, we conclude that there exists $\overline{\tau}$, defined by $N^*(\overline{\tau})^s = X_1$, such that (31) is satisfied for $\tau \in [0, \overline{\tau})$, provided that $s > 4\mu/(\mu-1)$. In this case, $B(\tau) < 0$ and (30) holds for $\tau \in [0, \overline{\tau})$.

Assume that $I = [0, \overline{\tau})$, with $\overline{\tau} \leq \tau^*$, is an interval in which condition (30) holds, and let us denote, without loss of generality, by X_l, $l = 1, 2$, the positive roots of $F(\cdot, \tau)$, for $\tau \in I$. We set $\omega_l = \sqrt{X_l}$, and we remember that ω_l depends on τ.

Let $\theta_l(\tau) \in [0, 2\pi]$, $\tau \in I$, be the unique solution of

$$\begin{aligned}
\cos(\theta_l(\tau)) &= \frac{(b_2 - a_1 b_1)\omega_l^4 + (a_1 b_3 - a_3 b_1 - a_2 b_2)\omega_l^2 - a_3 b_3}{b_1^2 \omega_l^4 + (b_2^2 - 2 b_1 b_3)\omega_l^2 + b_3^2}, \\
\sin(\theta_l(\tau)) &= \frac{b_1 \omega_l^5 + (a_1 b_2 - a_2 b_1 - b_3)\omega_l^3 + (a_2 b_3 - a_3 b_2)\omega_l}{b_1^2 \omega^4 + (b_2^2 - 2 b_1 b_3)\omega_l^2 + b_3^2}.
\end{aligned}$$

One can check, using (26) and (27), that $i\omega_c$, with $\omega_c = \omega_l(\tau_c) > 0$, satisfies $\Delta(i\omega_c, \tau_c) = 0$, and so is a pure imaginary characteristic root of (25), if and only if

$$\omega_l(\tau_c)\tau_c = \theta_l(\tau_c) + 2j\pi, \qquad \text{for some } j \in \mathbb{N},$$

that is, if τ_c is a root of the function Z_l^j, defined by

$$Z_l^j(\tau) = \tau - \frac{\theta_l(\tau) + 2j\pi}{\omega_l(\tau)}, \quad \tau \in I, \qquad \text{with } j \in \mathbb{N}.$$

The following theorem is due to Beretta and Kuang [10].

Theorem 5.2. *Assume that the function $Z_l^j(\tau)$ has a positive root $\tau_c \in I$ for some $j \in \mathbb{N}$. Then a pair of simple purely imaginary roots $\pm i\omega(\tau_c)$ of (25), with $\omega(\tau_c) > 0$, exists at $\tau = \tau_c$ and*

$$\operatorname{sign}\left\{\frac{dRe(\lambda)}{d\tau}\bigg|_{\lambda = i\omega(\tau_c)}\right\} = \operatorname{sign}\left\{2\omega(\tau_c)^2 + A(\tau_c)\right\} \operatorname{sign}\left\{\frac{dZ_l^j(\tau)}{d\tau}\bigg|_{\tau=\tau_c}\right\}. \tag{35}$$

We can easily observe that $Z_l^j(0) < 0$. Moreover, for all $\tau \in I$, $Z_l^j(\tau) > Z_l^{j+1}(\tau)$, with $j \in \mathbb{N}$. Therefore, if Z_l^0 has no root in I, then the functions Z_l^j have no root in I and, if the function $Z_l^j(\tau)$ has positive roots $\tau \in I$, for some $j \in \mathbb{N}$, there exists at least one root satisfying

$$\frac{dZ_l^j}{d\tau}(\tau) > 0.$$

We can conclude the existence of a Hopf bifurcation as stated in the next theorem.

Theorem 5.3. *Assume that condition (18) holds true, $T = 0$, and (30) is fulfilled on an interval $I = [0, \overline{\tau})$, with $\overline{\tau} \leq \tau^*$.*

(i) If the function $Z_l^0(\tau)$ has no positive root in I, then the steady-state (N^*, E^*) is locally asymptotically stable for all $\tau \in [0, \overline{\tau})$.

(ii) If the function $Z_l^0(\tau)$ has at least one positive root in I, then there exists $\tau_c \in I$ such that the steady-state (N^*, E^*) is locally asymptotically stable for $0 \leq \tau < \tau_c$ and becomes unstable for $\tau \geq \tau_c$, with a Hopf bifurcation occurring when $\tau = \tau_c$, if and only if $F(\cdot, \tau_c)$ has a positive root $\omega(\tau_c)^2$ such that

$$\frac{\partial F}{\partial X}(\omega(\tau_c)^2, \tau_c) > 0.$$

Proof. First, we prove (i). If $Z_l^0(\tau)$ has no positive root in I, the above remark on the properties of the Z_l^j functions implies that no Z_l^j function has roots in I. Consequently, the characteristic equation (25) has no pure imaginary root and, from Lemma 5.1, all eigenvalues of (25) have negative real parts. Therefore, the steady-state (N^*, E^*) is locally asymptotically stable for all $\tau \in [0, \overline{\tau})$.

Second, we prove (ii). If the function $Z_l^0(\tau)$ has at least one positive root in I, then there exists at least one $\tau_c \in I$ such that $Z_l^j(\tau_c) = 0$, for some $j \in \mathbb{N}$, and

$$\frac{dZ_l^j}{d\tau}(\tau_c) > 0.$$

For $\tau = \tau_c$, the characteristic equation (25) has a pair of simple conjugate pure imaginary roots $i\omega(\tau_c)$ (see Theorem 5.2), $\omega(\tau_c) > 0$ satisfying $F(\omega(\tau_c)^2, \tau_c) = 0$. We denote by τ_c the smaller $\tau \in I$ satisfying these properties. Then, for $\tau < \tau_c$, all eigenvalues of (25) have negative real parts so (N^*, E^*) is locally asymptotically stable, and it becomes unstable for $\tau = \tau_c$. A Hopf bifurcation occurs at (N^*, E^*) for $\tau = \tau_c$ if and only if

$$\left.\frac{dRe(\lambda)}{d\tau}\right|_{\lambda = i\omega(\tau_c)} > 0,$$

that is, from (35), if

$$2\omega(\tau_c)^2 + A(\tau_c) > 0.$$

Since $\omega(\tau_c)^2$ is a root of $F(\cdot, \tau_c)$, this condition is equivalent to

$$\frac{\partial F}{\partial X}(\omega(\tau_c)^2, \tau_c) > 0.$$

This concludes the proof. □

We now return to the case $T \neq 0$. In order to study the local asymptotic stability of the positive steady state (N^*, E^*) of (13) when both delays τ and T are nonzero, we first prove a result dealing with the sign of the real parts of characteristic roots of (21) in the next lemma.

Lemma 5.4. *If all roots of equation (25) have negative real parts for a given $\tau > 0$, then there exists a $T_c(\tau) > 0$ such that all roots of equation (21) have negative real parts when $T < T_c(\tau)$.*

Proof. Assume that equation (25) has no root with nonnegative real part for $\tau > 0$. Thus, equation (21) with $T = 0$ and $\tau > 0$ has no root with nonnegative real part.

Regard T as a parameter. Clearly, the left hand side of equation (21) is analytic in λ and T. Following Theorem 2.1 of Ruan and Wei [33], as T varies, the sum of the multiplicity of zeros of the left hand side of equation (21) in the open right half-plane can only change if a zero appears on or crosses the imaginary axis.

Since equation (21) with $T = 0$ has no root with nonnegative real part, there exists a $T_c(\tau) > 0$ such that all roots of equation (21) with $T < T_c(\tau)$ have negative real parts. □

Using Theorem 5.3, we obtain the next theorem dealing with the asymptotic stability of the steady state (N^*, E^*) of (13) when both time delays τ and T are nonzero.

Theorem 5.4. *Assume that condition (18) holds true.*

(1) If no $\tau \in [0, \tau^*)$ fulfills condition (30), then for any $\tau \in [0, \tau^*)$, there exists a $T_c(\tau) > 0$ such that the steady state (N^*, E^*) of system (13) is locally asymptotically stable when $T \in [0, T_c(\tau))$.

(2) If (30) is fulfilled on an interval $I = [0, \overline{\tau})$, with $0 < \overline{\tau} \leq \tau^*$, and the function $Z_l^0(\tau)$ has no positive root in I, then for any $\tau \in [0, \overline{\tau})$, there exists a $T_c(\tau) > 0$ such that the steady state (N^*, E^*) of system (13) is locally asymptotically stable when $T \in [0, T_c(\tau))$.

(3) If (30) is fulfilled on an interval $I = [0, \overline{\tau})$, with $\overline{\tau} \leq \tau^*$, and there exists $\tau_c < \overline{\tau}$ satisfying (ii) of Theorem 5.3, then for any $\tau \in [0, \tau_c)$, there exists a $T_c(\tau) > 0$ such that the steady state (N^*, E^*) of system (13) is locally asymptotically stable when $T \in [0, T_c(\tau))$.

Proof. The points (1) and (2) are straightforward, since with these assumptions all characteristic roots of (25) have negative real parts for $\tau \in [0, \tau^*)$ (respectively, $\tau \in [0, \overline{\tau})$). So we conclude with Lemma 5.4.

For (3), from Theorem 5.3 it follows that all roots of equation (25) have negative real parts when $\tau \in [0, \tau_c)$. We also conclude with Lemma 5.4. □

Remark 4. *When the Hopf bifurcation occurs, periodic solutions appear. Moreover, since all solutions of (13) are bounded (see Proposition 3.1), the instability of (N^*, E^*) can only be associated with oscillating solutions. Therefore, following the Hopf bifurcation, system (13) exhibits oscillating solutions.*

6 Discussion

We analyzed, in the previous sections, a mathematical model of stem cells dynamics, taking into account the action of growth factors (which are external factors) on cell proliferation. This model is based on the models of Mackey [23], Mackey and Rudnicki [28] and Bélair et al [9]. It consists of a system of two age structured partial differential equations, modelling the evolution of the stem cell population (divided in proliferating and resting cells), coupled with a delay differential equation describing the production of growth factors. The action of growth factors is supposed to modify the rate of apoptosis, the mortality in the proliferating phase. We reduced this system to a system of two delay differential equations, with two delays and a distributed delay.

The mathematical analysis first stressed basic properties of the solutions, such as positivity and boundedness. We then studied the stability of the two steady states of the reduced model. A necessary and sufficient condition for the global asymptotic stability of the first steady state, corresponding to the cells' dying out, was obtained using a Lyapunov function.

The analysis of the local asymptotic stability of the second steady state consisted in studying first the model when one delay is equal to zero, and then deduce the stability when both delays are nonzero using analytical tools. The stability study of the model with one delay equal to zero has been performed by determining the sign of real parts of eigenvalues of a characteristic equation with delay-dependent coefficients. It stressed the existence of a Hopf bifurcation that can destabilize the steady state and lead to the appearance of oscillating solutions.

In previous mathematical studies of hematopoietic stem cells dynamics, oscillating solutions have shown their importance in the understanding of some diseases affecting blood cells, known to exhibit oscillations of circulating blood cells (see, for example, [5, 6, 7, 9, 11, 15, 16, 23, 24, 30, 31, 32]). These diseases are called periodic hematological diseases [21]. They can affect all blood cell types (periodic chronic myelogenous leukemia [5, 31], cyclical neutropenia [11]) or only one blood cell type (autoimmune hemolytic anemia [9, 30], which affects red blood cells). Periods of the oscillations observed in patients may vary from few days (19-21 days for cyclical neutropenia) to months (70-80 days for chronic myelogenous leukemia). Periodic hematological diseases are originated from the pluripotent hematopoietic stem cell population, a mutation of one cell being brought throughout successive divisions.

Hence, the existence of oscillating solutions in models of hematopoietic stem cells can sometimes be related to periodic hematological diseases, as it can be found in [5, 6, 11, 31]. In this study, we showed that the influence of growth factors, which are exterior to the process of hematopoiesis, should not be neglected in stem cells dynamics, since it adds some information on the behavior of hematopoietic stem cells, and the action of growth factors can lead to the existence of oscillating solutions in the stem cell population.

Future works should investigate numerically the existence of oscillating solutions, as obtained for example in [5, 6, 11, 31]. The delay-dependent coefficients of the characteristic equation (21) may lead to stability switches [10], that would prove very rich dynamics of the model. This part will be strongly dependent on experimental data available, especially about growth factors. As they become more and more popular in biology, because of their influence on various medical process (they are primarily used for cure treatments), the literature now provides a lot of information and data about the way they act on stem cells differentiation.

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